REMARKS

Claims 1 to 18, 20 to 23, and 35 to 51 are pending in this application. Applicants propose to amend claims 1, 10, 17, 22, and 23, and to cancel claims 18, 19, 21, and 40. Claims 35 to 39 are withdrawn, and claims 24 to 34 were previously canceled. Applicants also propose to add new dependent claims 42 to 51. In particular, new claim 48 adds concepts of original independent claim 18 as a dependent feature to claim 1. New claim 49 adds concepts of original independent claim 21 as a dependent feature to claim 1. New claim 51 adds the concepts of both claims 18 and 21 as a dependent feature to claim 1.

The present amendments and new claims would add no new matter. In particular, the language in claim 1 relating to an infectious agent as a target is supported throughout the application, e.g., at page 47, lines 6 and 12, page 56, line 9, page 57, line 25, page 59, line 31, and page 61, line 24. The concept of a genetic marker of a subject as a target is described, e.g., at page 7, lines 18-25, page 47, line 7, page 57, line 25, page 60, line 1, and page 61, line 24. The language relating to the use of a biological or chemical molecule as a target is described, e.g., at page 7, line 22, and at page 58, line 10.

The language in new claim 42 relating to all probes being nucleic acids is supported in the application, e.g., at page 21, lines 17-19. The language in new claim 43 relating to the use of markers for therapeutic optimization factors of the subject or of an infectious agent as targets is supported in the application, e.g., at page 7, lines 27-31, at page 71, line 10, and at page 58, line 11. The language in new claim 44 relating to cancer, vascular, inflammatory, endocrine, metabolic, and autoimmune markers is supported in the application, e.g., at page 5, lines 23-24, and at page 60, lines 1-3. In new claim 45, the terms immunoglobulin, self-antigen, and antigen, are supported, e.g., at page 54, line 23, at page 52, line 10, and at page 7, lines 16-20, respectively. In new claim 46, the terms poison, drug, or a small organic or inorganic molecule, are supported, e.g., at page 58, line 10, at page 5, line 23, and at page 7, lines 23-24, respectively. In new claim 47, the terms virus, bacteria, fungus, and pathogenic plant are supported, e.g., at page 7, lines 21-22. New claims 48 to 50 are based on original claims 18 and 21, and the term

"protein," in the sense of a gene product, in new claim 48 is supported throughout the application.

Applicants respectfully submit that the proposed claim amendments and new claims set forth above would raise no new issues that would require further consideration and/or search. Applicants submit that these amendments would place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection under 37 C.F.R. § 1.116 (a).

Applicants sincerely appreciate the Examiner's willingness to conduct and take the time for a personal interview. Although no specific claim language was approved, Ms. Jacobs, Dr. Snider, the Examiner, and the undersigned discussed independent claims 1, 18, and 21, along with the prior art Balch and Persing patents, and the Examiner indicated that he would consider the proposed amendments, and if possible enter the amendments and allow the claims. Applicants agreed to provide a formal written response, with the claim amendments discussed at the interview, along with a supporting declaration. By the present proposed amendment, applicants seek to focus the examiner's attention on claim 1 by canceling all other independent claims (18 and 21), and capturing the basic concepts of claims 18 and 21 in new claims 48 to 51, which depend from claim 1.

35 U.S.C. § 112, Second Paragraph

Claims 1 to 17, 20 to 23, 40, and 41 have been rejected as allegedly unclear. In particular, the Office Action objects to the phrase "selected from the group comprising" as being improper Markush language. Applicants respectfully submit that no Markush language was intended, and that the claims were clear as written. However, in the interests of moving this application towards allowance, applicants have further clarified claims 1 and 10, and have canceled claims 21 and 40. Thus, this rejection can be withdrawn.

35 U.S.C. § 102

Claims 1 to 8, 11 to 18, and 41 have been rejected as being allegedly anticipated by Balch, U.S. Patent No. 6,083,763. Applicants traverse this rejection for the following reasons.

According to the Office Action (at page 3), Balch describes

> a method of determining [a] cause of one or more medical symptoms by obtaining a biological sample from subject, obtaining an array of different probes that selectively interact with target associated with different known cause of one or [sic] medical symptoms, applying sample to probes so they interact, detecting and analyzing and the device and system of using such an array (see whole document esp. abstract, col. 5 lines 16-30, particularly col. 8 & col. 34 lines 5-12). This reference discloses the use of probes which are nucleic acids, antigens or antibodies (see col. 1 lines 25-30). Also disclosed is testing human samples or DNA (see col. 33 line 57 & 66). Also disclosed is use of thiol or amino groups for covalent binding of ligands (see col. 21 line 35-40).

As discussed during the personal interview, applicants submit that the goal of their claimed invention and the goal of Balch's patent disclosure are very different. Balch focuses on complicated multiplexed, hierarchical, molecular arrays that can be used to analyze samples. Although Balch mentions the general concept of searching for the cause of a defined set of medical symptoms, he always limits the possible causes of symptoms to disease "organisms" (see, e.g., col. 1, lines 51-58, col. 4, lines 16-17, and col. 5, lines 20-23) or "pathogens" (col. 5, line 26), and fails to describe or suggest other possible causative agents. Balch focuses on the types of probes and how to make his devices, not on the specific targets, and certainly not on combinations of different types of targets.

On the other hand, applicants' methods focus on the types of targets and/or combinations of different types of targets. For example, claim 1 covers a method of determining a cause of a given medical symptom exhibited by a subject using an array of different probes or different sets of probes, wherein each probe or set of probes selectively interacts with a target associated with a different known cause of the one or more medical symptoms. The array must include (i) a first probe or set of first probes directed to a first target, wherein the first target includes one or more markers for one or more infectious agents known to cause the medical symptom; and (ii) a second probe or set of second probes directed to a second target, wherein the second target

includes one or more genetic markers of the subject or one or more biological or chemical molecules known to cause the medical symptom.

As amended, claim 1 clearly requires at least one probe (the second probe) directed to one or more targets that Balch does not even consider (genetic markers of the subject or a biological or chemical molecule), much less use, in combination with probes directed to an infectious organism. Nowhere have applicants found any suggestion in Balch to use probes directed to targets such genetic markers of the subject or biological or chemical molecules as possible causes of a medical symptom in combination with probes directed to infectious organisms.

The Office Action notes at page 6 that applicants have alleged, "Balch does not teach probes directed to targets such as self-antigens, poisons, or genetic disorders," but that Balch does indeed describe genetic disorders and toxins. Applicants submit that the quotation from applicant's last response does not include the complete context of applicants' earlier statement. It may well be that Balch describes "toxins" and genetic disorders, but never in the context of a possible causative agent for a medical symptom in an assay for multiple different targets as recited in applicants's amended claims.

For example, as far as Balch's recitation of the word "toxin" is concerned, this term appears only twice in the entire patent (once in the background) as part of a laundry list of possible ligands. Never once does Balch suggest using probes to detect both a toxin and an infectious agent as targets that cause a given medical symptom.

With respect to genetic disorders, Balch (at column 33, lines 50-66) describes assaying genetic disorders by using multiple nucleic acids complementary to known mutations of cystic fibrosis. It seems that for this set of probes to be used effectively, the diagnosis of cystic fibrosis must already have been made. Alternatively, Balch describes the use of multiple DNA probes complementary to known viral strains that cause sexually transmitted diseases (STD). Again, it appears that the diagnosis of STD must already have been made.

In each case, Balch is confirming or refining a diagnosis of a medical disease, e.g., cystic fibrosis or STD, not determining the cause of a medical symptom. Thus, Balch describes

disease-specific methods. Applicants' invention relates to symptom-specific methods. This difference is subtle, but extremely important in practice. When a patient arrives at a doctor's office, she does not complain that she has cystic fibrosis or an STD. Instead, she says she has a fever, a sore throat, a cough, or a headache. Contrary to his broad statements, Balch's assays cannot determine the cause of a medical symptom, because he is searching for a specific disease, not for a cause of a medical symptom. Only by assaying for multiple, different targets of possible causative agents in the same assay, as presently claimed in claim 1, can one have any hope of reliably determining the true cause of a given medical symptom.

For example, if a patient has a cough, e.g., a lower respiratory tract problem, the cause may be bacterial infection, a viral infection, an inflammation, a foreign biological or chemical molecule, a genetic cause, or any of the several other causes. Thus, according to the present invention a "respiratory tract symptom-specific" assay would have to include probes that can detect a reasonable number of agents that could be the cause of the cough to repeatably and accurately pinpoint the proper diagnosis. Nowhere does Balch or any other cited prior art suggest the combination of probes to at least two different possible targets that are known causes of a given medical symptom as presently claimed. Thus, Balch cannot anticipate applicants' claim 1, or claims 2-17, and 20, which depend from claim 1.

As further evidence that the method of claim 1 is different from the Balch patent, applicants submit the declaration of Dr. Andrew Onderdonk, the Director of the Clinical Microbiology Laboratory at Brigham and Women's Hospital and a Professor of Pathology at Harvard Medical School (copy attached as Exhibit A). Dr. Onderdonk is familiar with the presently claimed invention, and has reviewed the Balch patent. With respect to the Balch patent, Dr. Onderdonk states (Declaration at Paragraph 7):

> Although the Balch patent recites in passing the general notion of a diagnostic test for the cause of a defined set of symptoms (at column 5, lines 17-21), it is clear from the overall context and other portions of the text (e.g., column 34, lines 3-13) that Balch contemplates the use of an array of probes for one type of target, e.g., different infectious agents, such as various viral strains, or different genetic mutations, e.g., for cystic fibrosis, that are the cause of a specific disease. Thus, Balch describes at most a disease-specific array. Balch does not describe or suggest the use of symptom-specific array that includes different probes directed

to two or more very different types of targets that are known to cause a given medical symptom (but could be from various diseases) as recited in the proposed claims.

Thus, Dr. Onderdonk states, "Balch simply does not describe or suggest anything other than the concept of a disease-specific array for one type of target. The Jacobs application, which covers methods of using symptom-specific arrays is a significant improvement over this simple Balch concept" (Declaration at Paragraph 7). Dr. Onderdonk concludes, "[b]ased on my knowledge and experience, my review of the Balch patent, and my understanding of the invention in the Jacobs application as articulated in the proposed claims, I believe that the proposed claims cover an invention that is distinct from any subject matter disclosed in the Balch patent" (Declaration at Paragraph 6).

Based on the proposed clarifying amendments to claim 1, and the comments above, applicants submit that claim 1 is novel and non-obvious in view of Balch.

Original independent claim 18 was also rejected as allegedly anticipated by Balch. Claim 18 recites a method of determining the susceptibility of a subject to a cause one or more medical symptoms. To crystallize the issues in the present application, and without prejudice to pursuing the concepts embodied in original claim 18 in another application, applicants have proposed to cancel claim 18 and to add new claim 48, which encompasses the concept of determining the susceptibility of the subject to a cause of one or more medical symptoms, but in conjunction with the steps of claim 1. Thus, claim 48 depends from claim 1, and is patentable for at least the same reasons discussed above.

Furthermore, Balch simply does not describe any method of determining the susceptibility of a subject to a cause of a medical symptom. As used in the present application, the term "susceptibility" is used in its common definition, e.g., "open, subject, or unresistant to some stimulus, influence, or agency" (Webster's Ninth New Collegiate Dictionary) and refers to a subject's susceptibility to infections (see, e.g., page 55, lines 16-17). This concept is different from genetic testing to see if a patient is at risk for contracting some genetic disorder, and is simply not discussed in Balch.

Although Balch describes standard diagnostic tests of known genetic disorders, he does not link this type of testing to medical symptoms. For example, Balch does not describe any assay in which a subject's sample is tested for a genetic marker that indicates the subject would be either tolerant or susceptible to infection by a particular pathogen. Applicants respectfully submit that Balch does not anticipate, or render obvious, proposed new claim 48.

Based on applicants' comments and Dr. Onderdonk's declaration, applicants submit that Balch fails to anticipate claims 1 or 48, as amended. Claims 2 to 8, 11 to 17, 20, and 41, all depend from claim 1, and thus are patentable for at least the same reasons discussed above. Thus, Balch does not anticipate any of claims 1 to 8, 11 to 18, 20, or 41, and applicants respectfully request that the Examiner reconsider and withdraw this rejection, and not apply this rejection to any of the proposed new claims that depend from claim 1. Furthermore, applicants submit that their claims would not have been obvious in view of Balch (see also the Onderdonk Declaration at Paragraph 6).

35 U.S.C. § 103

Claims 9 and 11 have been rejected as being allegedly unpatentable over Balch in view of Au-Young et al., U.S. Patent No. 6,309,821. While the Office Action admits that Balch does not describe the use of samples from a deceased subject or the use of biopsies, Au-Young is said to describe such samples. Applicants submit that Au-Young adds nothing of relevance to the presently claimed invention, because Au-Young describes DNA encoding a PAC10 human homolog, and has nothing to do with methods or kits for determining a cause of one or more medical symptoms exhibited by a subject.

Even if one of ordinary skill in the art would have been motivated to apply Au-Young's suggested uses to Balch's assay, which applicants do not concede, Au-Young does not describe the features of applicants' claim 1 that Balch lacks discussed above with respect to the rejection over Balch alone. Therefore, claims 9 and 11, which depend from claim 1, are not rendered obvious by the combination of these patents.

Next, claims 21 to 23 have been rejected as being allegedly unpatentable over Balch in view of Persing et al., U.S. Patent No. 5,643,723. Applicants traverse this rejection for the following reasons.

Original independent claim 21 recites a method of determining a cause of one or more medical symptoms in a subject and assessing the suitability of one or more therapeutic agents to treat the cause of the symptoms. To focus the issues in the present application, and without prejudice to pursuing the concepts embodied in original claim 21 in another application, applicants have proposed to cancel claim 21 and to add new claim 49, which encompasses the concept of assessing the suitability of one or more therapeutic agents to treat the cause of the one or more medical symptoms, but in conjunction with the steps of claim 1. Thus, claim 49 depends from claim 1, and is patentable for at least the same reasons discussed above.

The Office Action admits that Balch does not describe therapeutic optimization factors, but alleges that Persing describes, "detecting *M. tuberculosis* mutants, particularly rifampin resistant, by using probes that target rpOB (see whole doc. esp. abstract)" (Office Action at page 6). According to the Office Action, "[o]ne of ordinary skill in the art would have [been] motivated to apply Persing et al's teachings of detecting drug resistance genes to Balch's detection method in order to detect patients who have drug resistant pathogens. It would have been *prima facie* obvious to detect drug resistance in pathogens as taught by Persing et al. in order to correctly confirm disease diagnosis such as TB and provide correct drug regimen" (id.).

As discussed during the personal interview, applicants respectfully disagree, and even more so given the proposed cancellation of claim 21 and addition of new claim 49.

Applicants' new claim 49 would recite a method of determining a cause of one or more medical symptoms in a subject (of claim 1) and add the element of assessing the suitability of one or more therapeutic agents to treat the cause of the symptoms. For this method, the array would further include a third probe or set of third probes directed to a third target, wherein the third target includes one or more markers for one or more therapeutic optimization factors.

Neither Balch nor Persing describes the use of a combination of the claimed first, second, and third different probes. Thus, even if Balch and Persing were combined as the Office Action

suggests, the resulting method would not have been applicants' claimed invention. As a result, applicants submit that new claim 49 is patentable, and request that the Examiner enter the proposed amendment and not reject this claim. Claims 22, 23, and 50, which would depend from claim 49, would be patentable for at least the same reasons. Claim 51, which depends from claim 48 and adds the features of claim 49, would also be patentable for the same reasons.

CONCLUSION

Applicants request that the Examiner enter the proposed amendments, reconsider and withdraw the present rejections, and allow all pending claims as amended. No fees are believed due. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 12877-006001.

Respectfully submitted,

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J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906